Association of Hepatitis C Virus (HCV) Infection and Human Leukocyte Antigens (HLA)

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Abstract

Back ground: Several previous reports on the association between hepatitis C virus (HCV) infection and certain human leukocyte antigens (HLA) have yielded controversial results.
Objectives: This study was conducted to explore the association of HCV infection and certain HLA in patients from Al-Ramadi Province.
Subjects and methods: Thirty two patients with chronic HCV infection as well as 64 apparently healthy individuals and 30 patients with clinically evident acute viral hepatitis, but HCV negative were enrolled in the present study which was conducted in Al-Ramadi city for the period from August/2004 to May/2006. HCV infection was diagnosed by detecting the anti-HCV antibody by enzyme-linked immunosorbant assay (ELISA) and confirmed by Immunoblot assay. Determination of HLAs was done by Microlymphocytotoxicity technique.
Results: The results revealed that the presence of HLA-DR5 (Odd ratio 2.7, P 0.022) and HLA-DQ2 (Odd ratio 3.1, P= 0.008), and the absence of HLA-DR7 (Inverse Odd ratio 3.2, P = 0.04) and HLA-DQ1 (Inverse Odd ratio 2.8, P= 0.012) were associated with significantly increased risk for HCV infection as compared to healthy controls. On the other hand, the presence of HLA-DR5 (Odd ratio 6.5, P= 0.005) and HLA-DQ2 (Odd ratio 5.1, P= 0.002), and the absence of HLA-DR7 (Inverse Odd ratio 4.8, P= 0.018) were significantly associated with increased risk for HCV infection.
Conclusion: Genetic predisposition may play a role in hepatitis C virus infection in patients from Al-Ramadi city.
Key words: Viral hepatitis, Hepatitis Cvirus. Human leukocyte antigens.

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Introduction

Hepatitis C virus is a positive stranded RNA and enveloped virus that classified recently within the genus *Hepacivirus* of the family *Flaviviridae*. Furthermore, there are at least 6 well known genotypes of the virus.[1] This worldwide distributed virus may cause 130-170 million people infections.[2] Chronic HCV infection was reported to be developed in 50-85% of infected people with associated risks of cirrhosis, liver failure and hepatocellular carcinoma. [3].

Multiple factors may influence the host-virus interaction in patients infected with HCV infection. Among host actors that have potential role in HCV infection and progression; earlier studies suggest that there may be an association between HLA such as HLA-DR3 and Italian HCV positive patients [4]. However, subsequent studies have yielded controversial results [5, 6,7]. On the

other hand, it has been found that subjects with certain HLA alleles (A*34, B* 56, DRB1* 1502) have significant lower HCV load, while patients with HLA-B* 4001 have significantly higher viral load [8, 9]. .Some other studies associated human leukocytes antigens and the infection with HCV to ethnic and/or geographic differences among subjects [10, 11 , 12,13,14]. Additionally, another study reported that sex, HCV genotype and HLA DRB play an important role in the curative effect of antiviral therapy [15]. Testing of 52,435 liver transplant recipients from 1995 through 2005 in USA, Harber, *et.al* [16] found significantly lower proportions of HLA-DRB1 heterozygosity among HCV-infected than uninfected cases. Furthermore, DRB1*0101 and DRB1* 0301 have been found to play a role in HCV clearance and persistence in Egyptian patients with hemophilia and hepatocellular carcinoma [17]. Moreover, it has been suggested that the presence of HLA-DRB1*1601and HLA-DQB1*0502 may provide protection against HCV infection [18].

Subjects and Methods

Thirty two HCV infected patients from AL-Ramadi Province were included in the present study. 16 (50%) were males, the mean age of patients was38.1± 16.8 years. Additionally, 64 age and sex matched HCV negative apparently healthy individuals were enrolled as healthy control; and 30 patients with clinically and biochemically evident hepatitis, but HCV negative were enrolled as patients control. The diagnosis of HCV infection was achieved by detection of anti-HCV antibody by third generation ELISA technique (Randox HCV, UK), and confirmed by immunoblot assay (LiaTek, Organon, Belgium).

The human leukocyte antigens included in the study were as follows; HLA-A1,A2, A3, A9, A11, A23, A24, A25, A26, A28, A29, A30, A33, A34, and HLA-A74. HLA-Bw4**, B5, Bw6**, B7, B8, B12, B13, B14, B15, B16, B17, B18, B21, B27, B35, B37, B38, B39, B 40, B41, B44, B45, B48, B49, B50, B51, Bw55, Bw56, B57, B62, B63, B64, B39+67, and HLA- B 45+76. HLA-Cw1, Cw2, Cw3, Cw4, Cw5, Cw6, Cw7, Cw8, and HLA-Cw6+7. HLA-DR1, DR2, DR3, DR4, DR5, DRw6, DR7, Dr8, Dr9, DR10, DR11, DR12, DR14, DR17, DR12+7, DR11+3, DR52, and HLA-DR 53.HLA-DQ1, DQ2, DQ3, and HLA-DQ4. Determination of HLAs was done by Microlymphocytotoxicity technique on separated lymphocytes as described by Doxiadis (1998)[19]The results were statistically analyzed.

Results

Comparing with healthy controls, the results revealed that the presence of HLA-DR5 [Odd ratio 2.7, P (Fisher's exact) = 0,022] was associated with significantly increased risk for HCV infection; However, upon adjusting the P value it failed to reach the level of statistical significance. Similarly, the absence of HLA-DR4 [Inverse odd ratio 3.2, P (Fisher exact) = 0.04] was associated with significantly increased risk for HCV infection, but it failed to reach the level of statistical significance upon adjusting the P value table (1).

On the other hand, the presence of HLA-DQ2 [Odd ratio 3.1, P (Fisher exact) = 0.008] was associated with significant increase in HCV infection even after adjusting the P value (P= 0.025). Similarly, the absence of HLA-DQ1 [Inverse odd ratio 2.8 P (Fisher exact) = 0.012] was associated with significantly increased risk for HCV infection and remain so even after adjusting the P value (0.037), table (2).

Comparing to patient control, the results found that the presence of HLA-DR5 [Odd ratio 6.2, P (Fisher's exact) = 0.005] was significantly associated with increased risk

for HCV infection; However, the adjusted P value was failed to reach the level of statistical significance table (3). While the presence of HLA-DQ2 [Odd ratio, P (Fisher's exact) = 0.002] was significantly associated with increased risk for HCV infection even after adjusting the P value (0.006), table (4). On the contrary, the absence of HLA-DR7 [Inverse Odd ratio 4.8, P (Fisher's exact) = 0.018] was associated with significantly increased risk for HCV infection, but the adjusted P value) was insignificant, table (3).

Table (1): Association of HLA-DR antigens with HCV status compared to healthy control.

HLA-DR antigen	Healthy control		HCV positive		Odd ratio	Inverse odd ratio	EF	PF	P value Fisher exact	Adjusted P value
	No.	%	No.	%						
1	16	25	5	15.6	0.6	1.8	**	0.111	NS	
2	14	21.9	7	21.9	1.0	**	**	**	NS	
3	15	23.4	6	18.8	0.8	1.3	**	0.058	NS	
4	16	25	3	9.4	0.3	3.2	**	0.173	0.043	NS
5	13	20.3	13	40.6	2.7	1.7**	0.255	**	0.022	NS
6	15	23.4	5	15.6	0.6	3.0	**	0.092	NS	
7	15	23.4	3	9.4	0.3	**	**	0.156	NS	
8	5	7.8	4	12.5	1.7	**	0.051	**	NS	
10	4	6.3	4	12.5	2.1	**	0.067	**	NS	
52	6	9.4	5	15.6	1.8	**	0.069	**	NS	
53	4	6.3	3	9.4	1.6	**	0.033	**	NS	
Blank	5	7.8	5	18.8						
Total	64	100	32	100						

Table (2): Association of HLA-DQ antigens with HCV status compared to healthy control.

HLA-DR antigen	Healthy control		HCV positive		Odd ratio	Inverse odd ratio	EF	PF	P value Fisher exact	Adjusted P value
	No.	%	No.	%						
1	36	56.3	10	31.3	0.4	2.8	**	0.364	0.012	0.037
2	29	45.3	23	71.9	3.1	**	0.486	**	0.008	0.025
3	28	43.8	12	37.5	0.8	1.3	**	0.100	NS	
Blank	35	54.7	19	59.4						
Total	64	100	32	100						

Table (3): Association of HLA-DR antigens with HCV status compared to patient control.

HLA-DR antigen	patient control		HCV positive		Odd ratio	Inverse odd ratio	EF	PF	P value Fisher exact	Adjusted P value
	No.	%	No.	%						
1	1	3.3	5	15.6	5.4	**	0.127	**	NS	
2	3	10	7	21.9	2.5	**	0.132	**	NS	
3	7	23.3	6	18.8	0.8	1.3	**	0.057	NS	
4	8	26.7	3	9.4	0.3	3.5	**	0.191	NS	
5	3	10	13	40.6	6.2	**	0.340	**	0.005	NS
6	3	10	5	15.6	1.7	**	0.062	**	NS	
7	10	33.3	3	9.4	0.2	4.8	**	0.265	0.018	NS
8	1	3.3	4	12.5	4.1	**	0.095	**	NS	
10	4	13.3	4	12.5	0.9	1.1	**	0.010	NS	
52	5	16.7	5	15.6	0.9	1.1	**	0.012	NS	
53	4	13.3	3	9.4	0.7	1.5	**	0.044	NS	
Blank	11	36.7	6	18.7						
Total	30	100	32	100						

Table (4): Association of HLA-DQ antigens with HCV status compared to patient control.

HLA-DR antigen	patient control		HCV positive		Odd ratio	Inverse odd ratio	EF	PF	P value Fisher exact	Adjusted P value
	No.	%	No.	%						
1	10	33.3	10	31.3	0.9	1.1	**	0.030	NS	
2	10	33.3	23	71.9	5.1	**	0.578	**	0.002	0.006
3	8	26.7	12	37.5	1.7	**	0.148	**	NS	
Blank	32		19							
Total	30	100	32	100						

Discussion

Results of the present study found that patients having HLA-DQ2 as compared to healthy and patient controls and the absence of HLA-DQ1 as compared to healthy control were significantly associated with high risk of HCV infection. The relevance of presence or absence of certain HLA alleles and HCV infection obtained in this study was consistent with previous reports [4,6,17]. Moreover, multiple studies have reported that class II alleles may play a role in the natural history of HCV infection [13,18,20] , and viral load [8], and even in the curative effect of antiviral therapy [13,15].

Some studies showed that presence of certain type of HLA alleles Class II had clearance effect on HCV infection while the same types of alleles were found to be influenced persistence HCV infection when tested in another race or population [21]. DQB1*0501 was reported to have clearance effect on HCV infection when tested in Irish [22] and American [23], but it had influenced persistence HCV in Puerto Rican [24]. The DRB1*0701 had influenced persistent HCV infection in Europeans [25] , Irish [26] and polish [27] ,while it had a viral clearance effect on Thai [28] patients. The same observations were reported with HLA Class-I when HLA-A03 had clearance effect on HCV infection in Irish [29] and American black [11] while it had influenced persistent HCV infection in Korean [10] ; HLA-B35 had clearance effect in Tunisian [30] but influenced persistence HCV in Korean [10] patients.

The above-mentioned controversy may be attributed to ethnic and geographic factors associated with HCV infection [11]. In recent report, it has been concluded the HCV genotypes and the genetic background of the innate and adaptive immune response may significantly affect the natural history of HCV infection [21].

Although the presence of HLA-DR5 and the absence of HLA-DR4 and HLA-DR7 were associated with significantly high risk of HCV infection as compared to healthy and patient control; however, they failed to reach the levels of statistical significance upon adjusting the P values. These results probably due to small sample size; therefore, further study on larger sample size is recommended to verified these results.

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